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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/079,834	05/15/1998	JOHN D. MOUNTZ	D6005	8770

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/079,834	MOUNTZ ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 7/1/04 has been entered. Claim 16 has been canceled. Claims 1, 3-6, and 8-9 are currently pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of pending claims 1, 3-6, and 8-9 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained in part. The rejection of previously pending claim 16 is withdrawn in view of the cancellation of claim 16. Also, applicant's amendment to claim 8 overcomes the lack of enablement for delivering genes to inhibit apoptosis to antigen presenting cells *in* vivo. Applicant's rejections as they apply to the remaining grounds of rejection have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The previous office action stated that the specification, while being enabling for:

> A method of inducing systemic T-cell tolerance to an antigen in an individual in need of such treatment, comprising the step of : administering to said individual peritoneal macrophages which (1) express high levels of Fas ligand resulting from co-infection with AdLoxPFasL and AdCANCre adenoviruses, (2) do not express Fas and (3) express said antigen, wherein said antigen presenting cells induce apoptosis of Fas-Positive T-cells directed towards said antigen resulting in said induction of systemic T-cell tolerance to said antigen.

;does not reasonably provide enablement for inducing systemic tolerance using antigen presenting cells other than fas-negative peritoneal macrophages.

The applicant argues that the references cited in the previous office action, namely Restifo, Seino et al., and Kang et al., are distinct from the present invention because the present invention requires the use of antigen-presenting cells. However, the term "antigen presenting cell" is broad and encompasses any cell type that can present antigen in the context of MHC class I or class II to a T cell. At the time of filing, it was well known that while MHC class II is only expressed on a subset of cells, known as professional antigen presenting cells, MHC class I is ubiquitously expressed in all types of normal cells with the exception of red blood cells. Thus, the claim as written read on the use of numerous types of cells that expresses MHC class I. The references cited in the previous office action all teach cell types which express MHC class I and antigen, including fibroblasts, epithelial cells, lymphomas, hepatocytes, and myocytes. In particular, Kang et al. and Zhang et al., both cited in the previous office action, teach the use of adenoviral vectors encoding FasL. The adenoviral vector transduced cells described in these references express not only FasL and MHC class I, but adenoviral

antigens as well. Thus, the cited references do in fact teach antigen presenting cells and are relevant to the enablement of the instant invention as claimed.

The applicant further argues that the references do not teach "fas negative antigen presenting cells" or the "transduction with combined adenoviruses" as instantly claimed. In regards to "fas negative antigen presenting cell", the applicant is directed to Seino et al. which utilized fas-negative antigen presenting cells in their experiments, including fas-negative baby hamster kidney cells and fas-negative T cell lymphoma cells. Kang et al., Zhang et al., and Murave et al., further teach the use of adenovirus and even inducible adenovirus encoding FasL. In response to the argument that the references cited do not teach the use of combined adenoviruses to express FasL as disclosed by the specification, the applicant is directed to Zhang et al. which in fact does teach the use of combined adenoviruses, AdLoxPFasL and AdCANCre. Furthermore, the publications cited in the previous office action were all cited as evidence of the state of the art of using FasL expression to inhibit graft rejection. Since this is an enablement rejection and not an art rejection under 35 U.S.C. 102 or 103, the cited references are not required to teach each and every element of the instant invention. Instead, the references are used to establish the level of predictability or lack thereof in the art at the time of filing. The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art.

Accordingly, what is known in the art provides evidence as to the question of predictability. See MPEP 2164.03 and *In re Marzocchi*, 439 F.2d 220, 22324, 169 USPQ 367, 369-70 (CCPA 1971). In the instant application, the cited references establish that at the time of filing, a controversy existed in the art as to the ability of FasL to inhibit graft rejection or induce T cell apoptosis. In a review of fas ligand which discusses a number of peer reviewed papers published at the time of filing between 1996 and 1998, Restifo discusses the fact that although the idea that fas ligand expression could grant immune privilege status rapidly gained popularity, substantial evidence to the contrary exists in the literature (Restifo (2000) Nature Med., Vol. 6 (5), 493-495). Numerous papers cited by Restifo document the fact that expression of recombinant fas ligand by many different cell types results in an inflammatory response *in vivo* rather than tolerance. Of specific note, Kang et al. demonstrated that islet cells, fibroblasts, epithelial cells, and various tumor cell lines genetically modified to express fas ligand are rapidly rejected *in vivo* as a result of a profound inflammatory response (Kang et al. (1998) Transp. Proceed. Vol. 30, page 538). Seino et al. also showed that fas-negative baby hamster kidney cells and fas-negative T lymphoma cells transfected with cDNA encoding fas ligand stimulated a substantial inflammatory response and were rapidly rejected *in vivo* (Seino et al. (1997) Transp. Proceed., Vol. 29, 1092-1093). Based on the data as a whole, Restifo concluded that ectopic expression of fas ligand on cells results in inflammation not immunosuppression (Restifo, page 493-494). The previous office action also cited Zhang et al. for demonstrating that inducible adenoviral FasL expression in hepatocytes and myoctyes induces inflammation and does not confer immune privilege (Zhang et al. (1998) J. Virol., Vol. 72 (3), 2484-2490,see page 2484, column1). Further, Murave et al.

was cited for teaching that transplantation of syngeneic pancreatic islets which have been transduced *ex vivo* with an adenovirus vector encoding Fas ligand rapidly lose function as a result of apoptosis and inflammatory immune responses (Murave et al. (1997) Human Gene Ther., Vol. 8, 955-963, page 960, column 2). Thus, the cited publications establish that the skilled artisan would have expected inflammation and not immunosuppression after transplantation of cells which have been modified to express fas ligand. As a result, the skilled would have considered it unpredictable that FasL expression an any antigen presenting cell would result in immunosuppression rather than inflammation *in vivo.*

The applicant also argues that the specification provides working examples which demonstrate that antigen presenting cells prepared according to the instant invention induce T cell apoptosis. In response, the previous office action pointed out that the specification and the declaratory evidence previously provided by the applicants only present data obtained using fas-negative peritoneal macrophages which have been infected *ex vivo/in vitro* with the AdLoxPFasL and AdCANCre adenoviruses. The working examples and declaratory evidence show that transplantation of these peritoneal macrophages can induce the apoptosis of the host T cells. Thus, while the specification broadly states that any antigen presenting cell expressing fas ligand can be used to induce T cell tolerance, the evidence of record only supports the use of fas-negative peritoneal macrophages. Based on the state of the art as discussed above, which demonstrated that FasL expression on other types of antigen presenting cells resulted in inflammation rather than immunosuppression, applicant's data generated using fas-negative peritoneal macrophages cannot be extrapolated to other types of antigen presenting cells. Thus, based on the evidence of record which is limited to fas negative peritoneal macrophages

which express fas ligand, and the teachings of the prior art that most antigen presenting cells which express fas ligand induce inflammation and not tolerance *in vivo*, it would have required undue experimentation to practice the scope of the claims as written.

The previous office action analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the art for the finding of a lack of enablement for the scope of the instant methods. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). 35 U.S.C. 112 also requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Based on the Wands analysis of the instant specification, see above, the scope of the instant claims does not bear a reasonable correlation to the scope of enablement provided by the specification and as such does not meet the requirements of 35 U.S.C. 112, first paragraph.

The rejection of claim 1 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of applicant's amendment to the claim.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER